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DEVELOPMENT OF AN ULTRA-FAST-CURING WOUND DRESSING

ANNUAL REPORT

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We are developing a drug-dispensing field wound dressing. The wound dressing, which can be easily applied by an untrained person, contains a coagulant to stop bleeding, and an antibiotic to prevent bacterial infection.

The medicated wound dressing is made of an ultra-fast-curing polyurethane oligomer which is designed to cure at room temperature and delivers drugs on a controlled, sustained and highly reproducible basis. Keywords:

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SUMMARY

Thermedics Inc., is developing a second-generation, drug-dispensing wound dressing. The wound dressing, which can be applied by the wounded soldier himself, incorporates thrombin as a coagulant, and gentamycin sulfate as a wide-spectrum antibiotic.

The new wound dressing is a trilaminate composite. The air side of the trilaminate is a fabric impregnated with an aliphatic, medical-grade polyurethane elastomer; the middle laminate is a controlled release layer, containing the microencapsulated pharmacoactive agents, and the third laminate is a 1.0-mil-thick layer of acrylic-based, pressure-sensitive adhesive.

The middle layer is fabricated from a mixture of urethane and silicone oligomers, which are precompounded with pharmacoactive agents, and is subsequently solidified (cured) upon mere exposure to low-intensity UV radiation at room temperature. Solidification at room temperature is a vital consideration, because most drugs are rapidly inactivated upon mild heating. Once cured, the oligomer layer containing pharmacoactive agents becomes a controlled-release monolith, capable of dispensing drugs at a continuous and predictable rate.

FOREWORD

Future conflicts may have to be fought without the advantage of overwhelming American air supremacy. In the absence of air supremacy, it may not be possible to evacuate wounded American soldiers for proper medical treatment for at least several days. This situation implies that a wounded soldier would need to be treated in the field; the initial treatment would have to be performed by himself, a buddy, or by a paramedic.

Based on this scenario, we embarked on the development of a new field wound dressing. The new field wound dressing would need to be applied without the benefit of prior medical training, during combat, and under all imaginable climatic conditions. Furthermore, the new wound dressing needs to incorporate coagulants and extended-action therapeutic agents to provide immediate stabilization of the wound. Currently available hospital wound dressings do not meet these requirements.

Under research contract DAMD17-83-C-3240, Thermedics is developing a second-generation wound dressing which speeds wound healing, incorporates pharmacoactive substances, and can be easily applied by the wounded soldier himself. This new wound dressing is based on an ultra-fast-curing liquid polyurethane oligomer. The oligomer can be easily precompounded with pharmacoactive agents and, subsequently, cured in less than seconds at room temperature by illumination with UV radiation. Following cure, the wound dressing delivers the pharmacoactive agents in a controlled, sustained-release basis.

This second-generation, medicated wound dressing, when properly developed and tested, may become an ideal vehicle for the initial wound stabilization of wounded soldiers. Our research is being aimed at the development of medicated wound dressing with the following characteristics:

- Oligomer cured at room temperature during manufacture; thus, even heat-sensitive drugs may be incorporated.
- The ready-to-use field wound dressing will be dispensed from waterproof kits carried in a standard-issue backpack.
- Field wound dressing may be applied under any conceivable climatic condition by nonmedical personnel.
- Dressing is highly compliant for physical comfort and is highly abrasion resistant, even when wet.
- Dressing is moisture permeable but does not permit penetration of water or bacteria.

- Dressing delivers medicaments or a controlled, predictable and sustained basis.

This unique combination of properties makes our new field wound dressing an innovative solution to the changing military priorities.

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I. MILITARY SIGNIFICANCE

Contingency plans for future conflicts place unique demands on the military which are not experienced in the civilian community. Contrary to the present treatment rendered to most casualties, it is most probable that soldiers wounded in future combat environments will face an entirely different situation. It will be common for evacuation of these patients to be delayed for 72 hours and possibly longer. During this critical post-wounding period, qualified medical personnel will not be immediately available to initiate therapy. It is during this crucial time that care will be self-administered or at best be provided by minimally trained perronnel.(1) It thus becomes critical that means be available to initiate therapeutic measures under these unusual circumstances.

Less than half the number of soldiers killed in battle die outright as a result of explosions or high-velocity missiles. The high morbidity and mortality associated with combat injuries is primarily attributable to post-wound medical complications, such as overwhelming infections and uncontrolled bleeding. Traditionally, wounds have been treated with dressings. Wound dressings are usually composed of sterile, absorbent cloth, pressure bandages, or a flat strip of elasticized, adhesive film, designed to cover and protect wounds.

The vast majority of maxillofacial wounds inflicted in combat are infected or become infected early on in their course of treatment.(2) Currently available wound dressings are primarily limited to gauze pressure bandages. These materials have minimal beneficial characteristics. They function as simple coverings that are not impervious to microorganisms, thereby providing little protection from infection. By being absorbent, they may tend to desiccate the wound, thus delaying healing. The material absorbed into the dressing may provide an excellent substrate supporting microbial growth. These materials may provide a mild measure of hemorrhage control by the application of pressure. However, pressure must be maintained for long periods, thereby restricting body movement so important in combat.

It is our intent to provide a compliant, thin, easily applied medicated wound dressing, dispensed from water-impermeable packages. The medicated wound dressing would be applied to maxillofacial wounds to stop bleeding and prevent bacterial infection, thus providing immediate stabilization of wounds until more definitive medical attention becomes available to the solider.

Under these circumstances, a wounded soldier can return to combat with the comforting knowledge that the wound dressing is delivering a precise, controlled, and reproducible amount of coagulant and antibiotic. Further, the highly compliant wound dressing will reduce abrasion pain and will not interfere with normal body movements.

II. TECHNICAL OBJECTIVE

We are developing a second-generation medicated dressing which will be designed to approximate the following ideal properties:

- Have the capability of being applied by untrained personnel under a wide range of adverse climatic conditions
- Be soft, pliable and closely mimic the mechanical properties of natural, intact skin
- Be able to control bleeding and infection, while protecting the wound from the external environment
- Should display good mechanical properties, and act as a physical barrier to bacterial penetration
- Have good adhesion to intact skin and be capable of staying on when immersed
- Be semi-occlusive to keep wounds moist and free of eschar formation, and to promote faster healing
- Should display minimal adhesion to the wound itself so it may be removed without causing harm to the healing wound
- Be able to maintain a sustained therapeutic antibiotic dose, while never reaching a toxic serum level

III. HYPOTHESIS

In combat, morbidity and mortality are directly proportional to the extent and depth of high-velocity missile wounds. Less than half the number of soldiers killed in battle die outright as a result of explosions or high-velocity missiles. The high morbidity and mortality associated with combat injuries are primarily attributable to post-wound medical complications, such as overwhelming infections and uncontrolled bleeding.

It is widely accepted that the most difficult wound to treat is one characterized by the presence of an established infection, devitalized tissue, and foreign-body contaminants. The presence of infection, devitalized tissue and foreign body contaminants characterize most of the untreated combat injuries suffered by military personnel during conflicts.

Debridement is the treatment of choice for wounds from trauma. When debridement is delayed, especially longer than six hours, the incidence of wound infection rises sharply. Under combat conditions, such treatment is rarely possible, and it is often many hours, and sometimes several days, before definitive surgical treatment can be administered. Therefore, a military need exists to develop a second-generation field wound dressing that will be medicated to prevent infection, control diffuse bleeding, and stabilize the wound site by protecting it from the external environment.

Our hypothesis is that a medicated wound dressing containing extended action coagulants and topical antibiotics will provide immediate wound stabilization in the field. Coagulants will control profuse bleeding; and the topical antibiotics, when used early, should reduce the incidence of wound infection when debridement is delayed. Thus, the use of medicated field wound dressings will effect wound stablilization through: (a) hemostasis, (b) controlling infection, and (c) promotion of normal wound healing mechanisms.

We hypothesize that hemostasis will be rapidly reached through the incorporation of a coagulant, such as Thrombostat® (lyophilized thrombin) or tannic acid. Infection control (from pathogenic bacteria and opportunistic invaders) will be accomplished by incorporation of wide-spectrum antibiotics such as gentamicin or clindamycin, neomycin and polymyxin B. Finally, promotion of normal wound healing mechanisms will be accomplished by the use of an abrasion-resistant, semi-occlusive polymeric membrane, which is: (a) noninflammatory and non-antigenic to the wound, (b) compliant as skin, (c) similar to skin in oxygen permeability, (d) similar to skin in water vapor transmission characteristics, and (e) impervious to bacteria.

IV. WORK TO DATE

In accordance with the provisions of Contract No. DAMD-17-83-C-3240, we have been supplying prototype samples of medicated field wound dressings to Dr. J. Vincent at USAIDR for in vivo evaluation. These prototype dressings contained either 8 mg or 16 mg of gentamicin sulfate with a Poly Ethylene Glycol (PEG) excipient, and were supplied as pre-sterilized, one-inch-square, unsupported, free films.

Results to date have been very encouraging, and are fully described below. Basically, Dr. Vincent reported a classical dose-response curve, with control (placebo) animals displaying a mean count of 2.1×10^7 cfu/in^2 (colony forming units per square inch) of Staphylococcus aureus (ATCC 12600) after 3 days; animals treated with dressings containing 8 mg of microencapsulated gentamicin sulfate had a mean count of 6.99×10^4 cfu/in^2; and, finally, animals treated with dressings containing 16 mg of microencapsulated gentamicin sulfate had a mean count of only 9.81×10^2 cfu/in^2.

General impressions to date are that wound dressings made under this program were very favorable, and conformed well to the wounds. The dressings were slightly friable which was expected, since they were fabricated without the TECOFLEX TS backing material to facilitate extraction of residual gentamicin. So far, the only problem detected in these studies was a tendency of the prototype dressings to adhere to the wounds causing disruption upon removal: this problem will be addressed in the next contract year.

According to the protocol selected at USAIDR, guinea pigs are anesthesized and the intrascapular area shaved and treated with a depilatory. After injection of 0.5 ml of mepivicaine HCl at the operative site, a full-thickness dissection, approximately one inch square, is performed. The surgical phase is followed by the innoculation of Staphylococcus aureus at a concentration of 3×10^{11} per ml. A total innoculation of 50 µl is given, resulting in a 1.5×10^9 cfu/in^2. All wounds are covered with polyethylene sheeting, and the animals are checked daily for three days inaeroscopically for induration, erythema, moisture, suppuration and dressing removal.

At the end of the third day, the quantitative sampling technique of Williamson and Klingman is used to determine accurately the wound microflora. This is accomplished by holding a 2-cm^2 sterile glass chamber to the wound surface, and scrubbing the site for one minute using a sterile Teflon policeman and a 1-ml solution of buffered Triton X-100. The wash fluid is aspirated, replaced with 1 ml of fresh scrub solution, and the process repeated. The animals are then euthanatized with an overdose of Nembutal.

A 0.1-ml aliquot of the scrub solution is serially diluted in tenfold increments and plated on Trypticase Soy Agar by the Spiral Plater System. Following incubation of plates, the bacteria are counted with a Laser Bacteria Colony Counter, and the number of microorganisms/in^2 are calculated. Results are reported as colony forming units per square inch.

Following the above protocol, the Thermedics' prototype wound dressings consisted of four groups as shown in Figure 1.

A bacterial count of 10^2 may well be optimal for a field wound dressing. Clinical evidence suggests that some bacteria in a three-day wound prevents or retards fungal infection, whereas complete elimination of bacteria may allow opportunistic infection.

The above data were compiled from one of the last experiments conducted at USAIDR on October 25-28, 1985. After the trials were concluded, all loaded wound dressings were placed individually in autoclave bags and heat sealed in preparation for transport to Thermedics for extraction and quantification of residual gentamicin sulfate. All wash solutions were serially diluted and plated with the spiral plates for bacterial count. In addition, after clotting, serum was harvested from blood samples for quantification of serum gentamicin. Results are given in Tables 1 through 4.

These excellent results encourage us to continue the development of gentamicin sulfate medicated field wound dressings. Gentamicin is a member of the aminoglycoside antibiotic group, which also includes streptomycin, neomycin, kanamycin, amikacin, tobramycin and netilmicin. These agents are primarily used for treatment of serious infections caused by gram-negative bacteria in which less toxic antibacterials are ineffective or contraindicated.

Gentamicin was isolated from the actinomycete Micromonospora purpurea and found to have a wide spectrum antibacterial effect.[3] In vitro tests have demonstrated gentamicin to be a bactericidal antibiotic active against Escherichia coli, Proteus species, Pseudomonas aeruginosa, species of the Klebsiella-Enterobacter-Serratia group. Citrobactacter species and Staphylococcus species (including penicillin- and methicillin-resistant strains). Most species of streptococci, particularly group D or viridans, and anaerobic organisms such as Bacteroides and Clostridium are resistant to gentamicin and the other aminoglycosides.[4]

Gentamicin is found naturally in three chemical forms known as gentamicin C, C_{1a} and C_2, and collectively referred to as gentamicin C, or by its trade name gentamicin. All elicit similar biologic activity, and their aminoglycosidic structures are depicted in Figure 2.

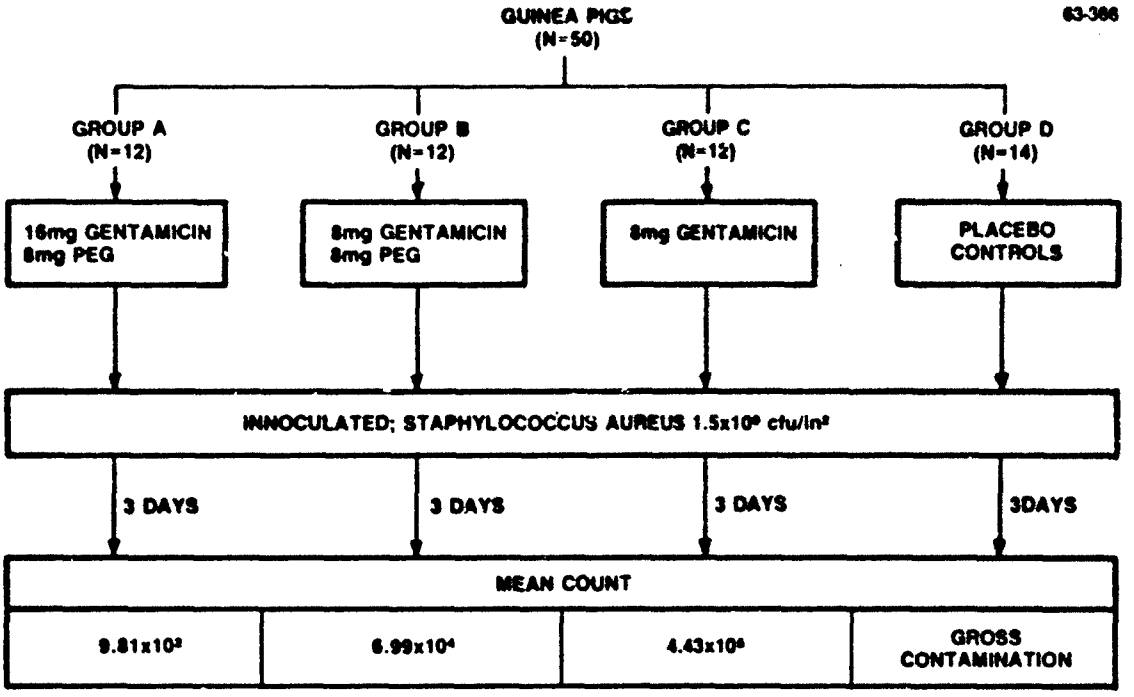

Figure 1. Experimental In Vivo Protocol

TABLE 1

NUMBER OF STAPHYLOCOCCUS AUREUS cfu/in^2,
REMAINING ON WOUND SURFACES
FOLLOWING TREATMENT WITH MEDICATED DRESSING

Group A (16 mg Gentamicin Sulfate; 16 mg PEG)

Animal No.	Wound Dressing Code Number	cfu/in^2	Serum Gentamicin
1	1464	3.51×10^3	0
2	1443	5.17×10^3	0
3	1592	2.07×10^3	0
4	1448	0	0
5	14235	0	0
6	1456	0	0
7	1384	0	0
8	1372	0	0
9	1320	1.03×10^3	0
10	1354	0	0
11	1283	0	0
12	1287	0	0

Mean Count = 9.81×10^2

TABLE 2

NUMBER OF STAPHYLOCOCCUS AUREUS cfu/in^2, REMAINING ON WOUND SURFACES FOLLOWING TREATMENT WITH MEDICATED DRESSING

Group B (8 mg Gentamicin Sulfate; 8 mg PEG)

Animal No.	Wound Dressing Code Number	cfu/in^2	Serum Gentamicin
13	1473	5.58×10^3	0
14	1487	2.21×10^5	0
15	1470	7.73×10^4	0
16	1474	2.48×10^3	0
17	1498	5.38×10^3	0
18	1483	4.14×10^3	0
19	1539	1.49×10^4	0
20	1534	1.77×10^4	0
21	1544	1.06×10^5	0
22	1566	1.83×10^5	0
23	1528	1.84×10^5	0
24	1369	1.85×10^4	0

Mean Count = 6.99×10^4

TABLE 3

NUMBER OF STAPHYLOCOCCUS AUREUS cfu/in^2,
REMAINING ON WOUNDED SURFACES
FOLLOWING TREATMENT WITH MEDICATED DRESSING

Group C (8 mg Gentamicin Sulfate)

Animal No.	Wound Dressing Code Number	cfu/in^2	Serum Gentamicin
25	1656	1.44×10^3	0
26	1659	1.13×10^4	0
27	1696	4.55×10^3	0
28	1652	2.07×10^3	0
29	1570	4.31×10^4	0
30	1583	8.45×10^4	0
31	1434	3.13×10^6	0
32	1454	5.83×10^4	0
33	1276	6.21×10^3	0
34	1279	2.52×10^5	0
35	1289	1.16×10^6	0
36	1284	5.63×10^5	0

TABLE 4

NUMBER OF STAPHYLOCOCCUS AUREUS cfu/in^2,
REMAINING ON WOUNDED SURFACES
FOLLOWING TREATMENT WITH PLACEBO (CONTROLS)

Group D (Placebo; Unmedicated Dressings)

Animal No.	Wound Dressing Code Number	cfu/in^2	Serum Gentamicin
37	Polyethylene Sheet	5.63×10^6	0
38	Unloaded Dressing	3.40×10^7	0
39	Ibid	Biopsy	0
40	Ibid	Biopsy	0
41	Ibid	Biopsy	0
42	Ibid	Gross Contamination	0
43	Ibid	4.66×10^7	0
44	Ibid	1.66×10^6	0
45	Ibid	Gross Contamination	0
46	Ibid	Gross Contamination	0
47	Ibid	Gross Contamination	0
48	Ibid	Gross Contamination	0
49	Ibid	1.8×10^7	0
50	Ibid	Biopsy	0

Mean Count of Six = 2.1×10^7

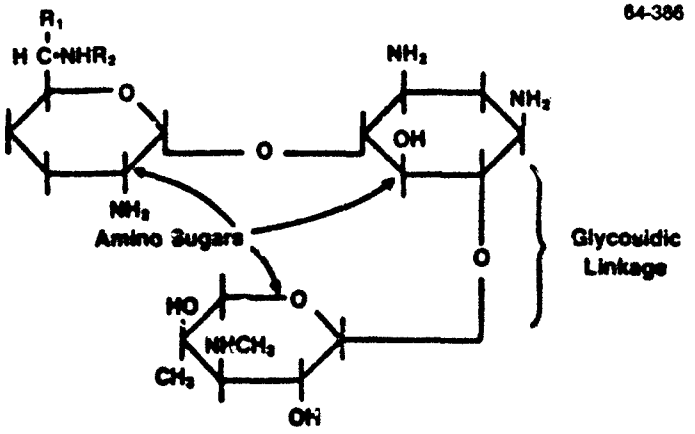

Figure 2. Chemical Structure of Gentamicin C (Gentamicin Powder; Schering-Plough, NJ)

Although it is an excellent antibiotic, the greatest single drawback to the wide use of gentamicin is its narrow therapeutic range. Serious infections require peak blood levels of 5 to 8 μg/ml, but levels of 10 to 12 μg/ml must be avoided because of an increased risk of ototoxicity[5] and nephrotoxicity. All studies agree that there is a very narrow range of blood levels between effective and toxic concentrations.[6-14]

We are fully aware of the potential ototoxicity and nephrotoxicity issues associated with systemic gentamicin therapy. However, in our case we are applying gentamicin on a local basis. Because the gentamicin is released in a controlled, timed-release basis (with no potential for dumping), we are able to maintain a therapeutic antibiotic dose for a sustained time on the wound surface, while never producing a toxic serum level. As our experiments indicate, serum levels of gentamicin in treated animals are undetectable; thus, neither ototoxicity nor nephrotoxicity are expected, even when treating the most extensive wounds.

Based on these considerations we propose to continue development of gentamicin-loaded wound dressings at an accelerated pace. Also, we are delighted to report that our association with Dr. J. Vincent, Dr. J. Setterstrom and Dr. G. Battistone at USAIDR has been exemplary. The close cooperation between Thermedics and USAIDR has made possible the independent verification of in vivo antibiotic activity of the prototype dressings. We look forward to maintaining, and deepening this relationship to rapidly and effectively develop wound dressings of value to combat medicine.

V. STATEMENT OF WORK

- TASKS 1 AND 2

  Produce sufficient quantities of vinyl-terminated urethane and silicone oligomers to fabricate pilot amounts of wound dressings.

- TASK 3

  Optimize the adhesion of the compounded urethane and silicone oligomers.

- TASK 4

  Incorporate microencapsulated gentamicin sulfate powder into the cured oligomeric mixture. Supply sufficient numbers of wound dressings with 2, 4, and 6 percent by weight of gentamicin sulfate to the USAIDR for testing and evalution.

- TASK 5

  Incorporate microencapsulated lyophilized thrombin powder into the uncured oligomeric mixture. Supply sufficient numbers of wound dressings with 100, 200, and 500 International Units (IU) of thrombin per gram of oligomeric mixture to the USAIDR for testing and evaluation.

- TASK 6

  Incorporate microencapsulated tannic acid into the uncured oligomeric mixture. Supply sufficient numbers of wound dressings with 2, 5, and 10 percent by weight of tannic acid to the USAIDR for testing and evaluation.

- TASK 7

  Supply wound dressings which contain both antibiotics and coagulant levels specified by the USAIDR.

- TASK 8

  Determine the in vitro elution kinetics of the antibiotic/coagulant wound dressing.

- TASK 9

  Quantitatively measure the oxygen, carbon dioxide and water vapor transmission rates of the cured wound dressing.

- TASK 10

  Determine the best packaging method of the wound dressing.

- TASK 11

  Evaluation of the effects of gamma radiation on the packaged wound dressing.

- TASK 12

  Conduct storage tests of the packaged and sterilized wound dressings.

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